zearalenone, cytochalasin, griseofulvin, ergochrome, cercosporin, marticin, xanthocillin, coumarins, tricothecenes, fusidanes, sesterpenes, amatoxins, malformin A, phallotoxins, pentoxin, HC toxin, psilocybin, bufotenine, lysergic acid, sporodesmin, pulcheriminic acid, sordarins, fumonisins, ochratoxin A, and fusaric acid.

With some certain embodiments of aspects of the invention, the secondary metabolite is a modulator of cell surface receptor signaling or a biosynthetic intermediate thereof. The term "cell surface receptor" is as used before. Modulators of cell surface receptor signaling might function by one of several mechanisms including, without limitation, acting as agonists or antagonists, sequestering a molecule that interacts with a receptor such as a ligand, or stabilizing the interaction of a receptor and molecule with which it interacts. Preferred modulators of cell surface signaling include, without limitation, the insulin receptor agonist L-783,281 and the cholecystokinin receptor antagonist asperlicin.

In certain embodiments of aspects of the invention, the secondary metabolite is a plant growth regulator or a biosynthetic intermediate thereof. A "plant growth regulator" is a molecule that controls growth and development of a plant by affecting processes that include, without limitation, division, elongation, and differentiation of cells. Preferred plant growth regulators include, without limitation, cytokinin, auxin, gibberellin, abscisic acid, and ethylene.

In certain embodiments of aspects of the invention, the secondary metabolite is a pigment or a biosynthetic intermediate thereof. A "pigment" is a substance that imparts a characteristic color. Preferred pigments include, without limitation, melanins and carotenoids.

In certain embodiments of aspects of the invention, the secondary metabolite is an insecticide or a biosynthetic intermediate thereof. An "insecticide" is a molecule that is toxic to insects. Preferred insecticides include, without limitation, nodulisporic acid.

In certain embodiments of aspects of the invention, the secondary metabolite is an anti-neoplastic compound or a biosynthetic intermediate thereof. An "anti-neoplastic" compound is a molecule that prevents or reduces tumor formation. Preferred anti-neoplastic compounds include, without limitation, taxol (paclitaxel) and related taxoids.

The phrase "increased activity" is used herein to refer to a characteristic that results in an augmentation of the inherent negative or positive function of the regulatory protein.

The invention provides variant regulator proteins of secondary metabolite production with increased activity and methods of producing the same. The invention further provides for the identification of specific amino acid residues that are important to the functioning of secondary metabolite regulator proteins. By way of non-limiting example, variant regulator proteins of the secondary metabolite regulator lovE are presented herein.

As known to those skilled in the art, certain substitutions of one amino acid for another may be tolerated at one or more amino acid residues of a wild-type regulator protein absent a change in the structure, activity and/or function of the wild-type protein. Such substitutions are referred to in the art as "conservative" substitutions, and amino acids may be categorized into groups that identify which amino acids may be substituted for another without altering the structure and/or function of the protein.

As used herein, the term "conservative substitution" refers to the exchange of one amino acid for another in the same conservative substitution grouping in a protein sequence. Conservative amino acid substitutions are known in the art and are generally based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. In a preferred embodiment, conservative substitutions typically include substitutions within the following groups: Group 1: glycine, alanine,

and proline; Group 2: valine, isoleucine, leucine, and methionine; Group 3: aspartic acid, glutamic acid, asparagine, glutamine; Group 4: serine, threonine, and cysteine; Group 5: lysine, arginine, and histidine; Group 6: phenylalanine, tyrosine, and tryptophan. Each group provides a listing of amino acids that may be substituted in a protein sequence for any one of the other amino acids in that particular group.

As stated *supra*, there are several criteria used to establish groupings of amino acids for conservative substitution. For example, the importance of the hydropathic amino acid index in conferring interactive biological function on a protein is generally understood in the art (Kyte and Doolittle, *Mol. Biol.* **157:**105-132 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. Amino acid hydrophilicity is also used as a criteria for the establishment of conservative amino acid groupings (see, *e.g.*, U.S. Patent No. 4,554,101).

Information relating to the substitution of one amino acid for another is generally known in the art (see, *e.g.*, Introduction to Protein Architecture : The Structural Biology of Proteins, Lesk, A.M., Oxford University Press; ISBN: 0198504748; Introduction to Protein Structure, Branden, C.-I., Tooze, J., Karolinska Institute, Stockholm, Sweden (January 15, 1999); and Protein Structure Prediction: Methods and Protocols (Methods in Molecular Biology), Webster, D.M.(Editor), August 2000, Humana Press, ISBN: 0896036375).

In one embodiment of the first aspect, the invention provides an improved regulator protein comprising an amino acid sequence coding for a variant of the lovE protein having at least one specific mutation that gives rise to greater transcription-activating properties of the regulator protein and/or increased lovastatin synthesis.

By way of non-limiting example, certain amino acid residues and mutations thereof in the lovE regulatory